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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,079	PECKER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-22* is/are pending in the application.

4a) Of the above claim(s) *16-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This SUPPLEMENTAL ACTION hereby replaces the Action mailed 1/13/05.

2. Applicant's amendment filed 6/28/04 and Applicant's response filed 10/29/04 are acknowledged and have been entered.

3. Applicant's election of SEQ ID NO: 1 as the species of polynucleotide sequence encoding a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3, SEQ ID NOs: 6 and 7 as the species of pair of oligonucleotides comprising a sense oligonucleotide and an antisense oligonucleotide, and light emitting moiety as a species of specific detectable moiety in Applicant's said response filed 10/29/04 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that newly submitted claims 16-22 are directed to an invention that is independent or distinct from the invention originally claimed for the reasons enunciated in the Restriction Requirement mailed 10/13/04. Accordingly, as enunciated in the said Restriction Requirement, claims 16-22 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 4-15 read on the elected species and are currently being examined.

The following are new grounds of rejection necessitated by Applicant's amendment filed 6/28/04.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 4-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendatory material not disclosed in the specification and claims as originally filed is "to at least a portion of SEQ ID NO: 3" and "wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification", i.e., in the context of "a polynucleotide sequence encoding a polypeptide sequence at least 90%

homologous to at least a portion of SEQ ID NO: 3, wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification". The instant application discloses that U.S. Patent No. 5,968,822 is incorporated by reference in the instant application. However, the disclosure in '822 (parent application serial no. 08/922,170) is that the polynucleotide fragment according to the invention may include any part of SEQ ID NO: 9 (1721 nucleic acid polynucleotide, SEQ ID NO: 1 of the instant application) which encodes a polypeptide having the heparanase catalytic activity, and that any polynucleotide sequence which encodes a polypeptide having heparanase activity, most preferably at least 90% homology with SEQ ID NO: 10 (543 amino acid long sequence, SEQ ID NO: 3 of the instant application), is within the scope of the invention (especially column 12 at lines 21-48, which Applicant cites for support for the amendment to instant claim 4). There is no disclosure in the instant application, nor in '822 of 'a polynucleotide sequence encoding a polypeptide sequence at least 90% homologous ***to at least a portion of*** SEQ ID NO: 3'.

6. Claims 4, 7-10, 12, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at thetime of invention of the claimed pair of oligonucleotides/kit thereof comprising a sense and an antisense oligonucleotide, being capable of directing PCR amplification resulting in a polynucleotide sequence encoding a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3 wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification, including the oligonucleotides in claims 7-10, 12, 14 and 15, and which polypeptide sequence may not have β-D-endoglucuronidase, i.e., heparanase, activity on heparin or heparin sulfate substrates.

The instant claims oligonucleotides/kit thereof that direct PCR amplification of a polynucleotide sequence that encodes a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3, i.e., a polynucleotide sequence of undisclosed length and sequence that encodes a polypeptide sequence of undisclosed length and sequence that has 90% homology to some portion of SEQ ID NO: 3 and which polypeptide and/or portion may not have β-D-endoglucuronidase, i.e., heparanase, activity on heparin or heparin sulfate substrates. There is insufficient disclosure in the specification for said oligonucleotides.

The specification discloses that the cloning and expression of human heparanase gene are described in US Patent No. 5,968,822, incorporated by reference in the instant application (page 4 at lines 13-16). The specification further discloses that the protein product of the said human gene is 61-63kDa (page 4 at lines 25-28 and page 5 at lines 25-28), and that heparanase activity was measured as the ability to degrade HS at specific intrachain sites, i.e., β-D-endoglucuronidase activity (column 1 of '822 at lines 66-67). The specification discloses that the heparanase nucleic acid is SEQ ID NO: 1 and 3 (page 27 at lines 10-13) and that SEQ ID NO: 4 and 5 are sense and antisense primers, respectively for SEQ ID NO: 1 and 3 (page 27 at lines 16-20) and that total RNA in various cell types was reverse transcribed and amplified using the cDNA primers SEQ ID NO: 6 and 7 (page 30 at lines 10-13). The disclosure in '822 (parent application serial no. 08/922,170) is that the polynucleotide fragment according to the invention may include any part of SEQ ID NO: 9 (1721 nucleic acid polynucleotide, SEQ ID NO: 1 of the instant application) which encodes a polypeptide having the heparanase catalytic activity, and that any polynucleotide sequence which encodes a polypeptide having heparanase activity, most preferably at least 90% homology with SEQ ID NO: 10 (543 amino acid long sequence, SEQ ID NO: 3 of the instant application), is within the scope of the invention (especially column 12 at lines 21-48). '822 further discloses SEQ ID NO: 6 of the instant application is used in PCR with a 21-mer C-terminal deleted version of the 24-mer SEQ ID NO: 7 of the instant application (column 16 of '822 at lines 23-37), and SEQ ID NO: 7 of the instant application is used in combination with PCR primer HPL229, and subsequently primer HPL171 is used with primer AP2 (column 15 of '822 at lines 51-67).

There is no disclosure in the instant application, nor in '822 of 'a polynucleotide sequence encoding a polypeptide sequence ***at least 90% homologous to at least a portion of*** SEQ ID NO: 3'. There is no disclosure in the instant application, nor in '822 of a pair of oligonucleotides that are sense/antisense PCR primers, except for those pairs SEQ ID NO: 4/5 and SEQ ID NO: 6/7, that direct PCR amplification of the polynucleotide set forth in SEQ ID NO: 1 that encodes the polypeptide consisting of SEQ ID NO: 3 and that has β-D-endoglucuronidase, i.e., heparanase, activity on heparin or heparin sulfate substrates, or those other aforementioned pairs of primers disclosed in '822. There is no disclosure of how a polynucleotide sequence or a partial sequence relates to primer sequence structure, including those that result in the polynucleotide sequence being the most prevalent polynucleotide product of the PCR amplification, and there is no disclosure of which oligonucleotide sequences correspond to directing PCR amplification of a polynucleotide sequence that encodes an unknown polypeptide sequence that is at least 90%homologous to at least a portion of the known polypeptide sequence SEQ ID NO: 3.

Evidentiary reference RT-PCR Methods & Applications Book 1 teaches that primer design can include those perfect sequence primers that exactly match the cDNA template, or those that do not. With regard to the former, the location of the primer template within the cDNA sequence is important because it defines the length of the PCR product, the primer location defines the distance that the cDNA must be extended from the 3' end of the mRNA to provide the 5' primer template, and the primer locations can be designed to distinguish between PCR

products derived from cDNA and products derived from contaminating genomic DNA. The said evidentiary reference further teaches that it is desirable to avoid designing primers that span a region of the mRNA where stable stem structures that can impede reverse transcription can form. In addition, the PCR primers should typically be between 22 and 30 nucleotides long and have an A/T content about equal to the G/C content, so that the optimal annealing temperature of both primers is similar, and primer sequences that can form stable inter-or intra-strand base pairing must be avoided. The said evidentiary reference teaches that even with several computer software programs to facilitate primer design, construction of successful PCR primers is empirical, and more than one primer set may need to be tested before a good combination is found, and that even under carefully optimized conditions, PCR often results in the generation of non-specific products due to amplification of alternatively spliced transcripts or from non-specific primer annealing (pages 10-15).

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as "A pair of oligonucleotides...being capable of directing PCR amplification resulting in a polynucleotide sequence encoding a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3, wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification", is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of directing PCR amplification to a polynucleotide sequence of undisclosed structure that encodes a polypeptide of undisclosed structure that is at least 90% homologous to at least a portion of SEQ ID NO: 3 which may not have heparanase catalytic activity. It does not specifically define any of the compounds that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others, and it does not define the portion of SEQ ID NO: 3 that has β-D-endoglucuronidase, i.e., heparanase, activity on heparin or heparin sulfate substrates, nor that the polypeptide must have said heparanase activity, nor does it describe how a polynucleotide sequence or a partial sequence relates to primer sequence structure, including those that result in the polynucleotide sequence being the most prevalent polynucleotide product of the PCR amplification. There is no disclosure of a polypeptide sequence at least 90% homologous to SEQ ID NO: 3 or to at least a portion of SEQ ID NO: 3 that other than an N-terminal truncation fragment of SEQ ID NO: 3 that lacks the putative signal peptide. SEQ ID NO: 3 is 543 amino acid residues in length, so 90% homologous to the entire polypeptide constitutes approximately 54 amino acid residues or less that can be altered, substituted or deleted, or amino acid residues may be added. There are 20 natural amino acid residues, so the genus would include 54^{20} possible members if the entire SEQ ID NO: 3 is considered; if a portion of SEQ ID NO: 3 is considered, then the genus would include an infinite number of members.

One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in the amendment filed 6/28/04 have been fully considered, but are not persuasive. Applicant's arguments are of record in the said amendment on pages 6-8, and are largely directed to the previous rejection of record.

With regard to argument relevant to the instant rejection, it is the Examiner's position that the '822 patent does not provide description for the reasons enunciated supra.

7. Claims 4, 7-10, 12, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how make and or/use the claimed pair of oligonucleotides/kit thereof comprising a sense and an antisense oligonucleotide, being capable of directing PCR amplification resulting in a polynucleotide sequence encoding a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3 wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification, including the oligonucleotides in claims 7-10, 12, 14 and 15. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass oligonucleotides/kit thereof that direct PCR amplification of a polynucleotide sequence that encodes a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3, i.e., a polynucleotide sequence of undisclosed length and sequence that encodes a polypeptide sequence of undisclosed length and sequence that has 90% homology to some portion of SEQ ID NO: 3 and which portion may not have β-D-endoglucuronidase, i.e., heparanase, activity on heparin or heparin sulfate substrates. There is insufficient disclosure in the specification for said nucleic acid molecules.

The specification discloses that the cloning and expression of human heparanase gene are described in US Patent No. 5,968,822, incorporated by reference in the instant application (page 4 at lines 13-16). The specification further discloses that the protein product of the said human gene is 61-63kDa (page 4 at lines 25-28 and page 5 at lines 25-28), and that heparanase activity was measured as the ability to degrade HS at specific intrachain sites, i.e., β-D-endoglucuronidase activity (column 1 of '822 at lines 66-67). The specification discloses that the heparanase nucleic acid is SEQ ID NO: 1 and 3 (page 27 at lines 10-13) and that SEQ ID NO: 4 and 5 are sense and antisense primers, respectively for SEQ ID NO: 1 and 3 (page 27 at lines 16-20) and that total RNA in various cell types was reverse transcribed and amplified using the cDNA primers SEQ ID NO: 6 and 7 (page 30 at lines 10-13).

The disclosure in '822 (parent application serial no. 08/922,170) is that the polynucleotide fragment according to the invention may include any part of SEQ ID NO: 9 (1721 nucleic acid polynucleotide, SEQ ID NO: 1 of the instant application) which encodes a polypeptide having the heparanase catalytic activity, and that any polynucleotide sequence which encodes a polypeptide having heparanase activity, most preferably at least 90% homology with SEQ ID NO: 10 (543 amino acid long sequence, SEQ ID NO: 3 of the instant application), is within the scope of the invention (especially column 12 at lines 21-48). '822 further discloses SEQ ID NO: 6 of the instant application is used in PCR with a 21-mer C-terminal deleted version of the 24-mer SEQ ID NO: 7 of the instant application (column 16 of '822 at lines 23-37), and SEQ ID NO: 7 of the instant application is used in combination with PCR primer HPL229, and then subsequently primer HPL171 is used with primer AP2 (column 15 of '822 at lines 51-67).

There is no disclosure in the instant application, nor in '822 of 'a polynucleotide sequence encoding a polypeptide sequence ***at least 90% homologous to at least a portion of*** SEQ ID NO: 3'. There is no disclosure in the instant application, nor in '822 of a pair of oligonucleotides that are sense/antisense PCR primers, except for those pairs SEQ ID NO: 4/5 and SEQ ID NO: 6/7, that direct PCR amplification of the polynucleotide set forth in SEQ ID NO: 1 that encodes the polypeptide consisting of SEQ ID NO: 3 and that has β-D-endoglucuronidase, i.e., heparanase, activity on heparin or heparin sulfate substrates, or those other aforementioned pairs of primers disclosed in '822. There is no disclosure of how a polynucleotide sequence or a partial sequence, i.e., "a polynucleotide sequence encoding a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3", relates to primer sequence structure, including those that result in the polynucleotide sequence being the most prevalent polynucleotide product of the PCR amplification.

The specification further discloses heparanases possessing widely disparate amino acid sequences, for example those cited on page 8 at lines 16-18 of the instant application, i.e., mouse B16-10 heparanase, human platelet heparanase, heparanases produced by several human tumor cell lines and CHO cells.

There is no disclosure in the instant specification as to which amino acid residues at which positions comprise heparanase binding sites, or which amino acid residues at other positions are tolerant of allowing the heparanase binding sites to function.

Evidentiary reference RT-PCR Methods & Applications Book 1 teaches that primer design can include those perfect sequence primers that exactly match the cDNA template, or those that do not. With regard to the former, the location of the primer template within the cDNA sequence is important because it defines the length of the PCR product, the primer location defines the distance that the cDNA must be extended from the 3' end of the mRNA to provide the 5' primer template, and the primer locations can be designed to distinguish between PCR products derived from cDNA and products derived from contaminating genomic DNA. The said evidentiary reference further teaches that it is desirable to avoid designing primers that span a region of the mRNA where stable stem structures that can impede reverse transcription

can form. In addition, the PCR primers should typically be between 22 and 30 nucleotides long and have an A/T content about equal to the G/C content, so that the optimal annealing temperature of both primers is similar, and primer sequences that can form stable inter-or intra-strand base pairing must be avoided. The said evidentiary reference teaches that even with several computer software programs to facilitate primer design, construction of successful PCR primers is empirical, and more than one primer set may need to be tested before a good combination is found, and that even under carefully optimized conditions, PCR often results in the generation of non-specific products due to amplification of alternatively spliced transcripts or from non-specific primer annealing (pages 10-15).

There is no disclosure of a polypeptide sequence at least 90% homologous to SEQ ID NO: 3 or to at least a portion of SEQ ID NO: 3 that other than an N-terminal truncation fragment of SEQ ID NO: 3 that lacks the putative signal peptide. SEQ ID NO: 3 is 543 amino acid residues in length, so 90% homologous to the entire polypeptide constitutes approximately 54 amino acid residues or less that can be altered, substituted or deleted, or amino acid residues may be added. There are 20 natural amino acid residues, so the genus would include 54^{20} possible members if the entire SEQ ID NO: 3 is considered; if a portion of SEQ ID NO: 3 is considered, then the genus would include an higher number of members. The claims encompass both.

The predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain function and properties requires a knowledge of, and guidance with regard to which amino acid residues at which positions in the amino acid sequence, if any are tolerant to modification and which are intolerant to modification, and detailed knowledge of the ways in which the product's structure relates to its function. Evidentiary reference Ngo et al (The Protein Folding Problem and Tertiary Structure Prediction, Merz & LeGrand, Birkhauser Boston, pages 491-495, 1994, entire article, especially Section 6, paragraph 1) teaches that the relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are therefore not predictable.

Because of this lack of guidance and the extended experimentation that would be required to determine which sequences and/or substitutions would be acceptable to produce/or retain functional activity, it would require undue experimentation for one of skill in the art to arrive at amino acid sequences that would have functional activity, and hence the nucleic acid molecules that encode them and the oligonucleotide primers that can be designed to PCR amplify them, especially in light of the disclosure of evidentiary reference RT-PCR Methods & Applications Book 1, i.e., although the base claims recite SEQ ID NO: 3, a known amino acid sequence with heparanase activity, the said claims recite that the pair of oligonucleotide primers must be capable of directing PCR amplification resulting in a polynucleotide of unknown structure that encodes a polypeptide of unknown structure that is at least 90% homologous to at least some unknown portion of SEQ ID NO: 3, and which may not have heparanase activity, and the said polynucleotide sequence must be the most prevalent polynucleotide product of the said PCR amplification. In addition, in Amgen v. Chugai, 18

USPQ 2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required on one of skill in the art for the determination of other nucleic acid sequences that are embraced by the claim. This is the situation under consideration. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make their corresponding nucleic acids.

Undue experimentation would be required of one skilled in the art to make and/or use (including use as a therapeutic agent) the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments in the amendment filed 6/28/04 have been fully considered, but are not persuasive.

Applicant's arguments are of record in the said amendment on pages 8-9, briefly that the target polynucleotide sequence for amplification is structurally defined as one "encoding a polypeptide sequence at least 90% homologous to at least of portion of SEQ ID NO: 3, wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification", that the instant application discloses use of SEQ ID NO: 6 and 7 as directing PCR amplification, and that since the target polynucleotide sequence for amplification is now structurally defined, alternative pairs of primers capable of directing PCR amplification can be readily constructed using standard methods well known in the art. (Applicant on page 9 actually refers to the recitation of claim 4 as "encoding at least a portion of a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3, wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification." The Examiner points out that "encoding at least a portion of a polypeptide" is not recited in claim 4, but rather "encoding a polypeptide sequence" is recited.

It is the Examiner's position that the use of the polynucleotide sequence for amplification is not structurally defined since it encodes a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO: 3, which portion not being defined, and which portion not being defined as having β-D-endoglucuronidase activity on heparin or heparin sulfate substrates, as enunciated supra in the instant rejection.

8. For the purpose of prior art rejections, the filing date of the instant claims 4-15 is deemed to be the filing date of the instant application, i.e. 10/2/03, as the parent applications do not support the claimed limitations of the instant application as enunciated in item #4 supra.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/11798 A1.

WO 99/11798 A1 teaches the PCR primers HPU-355 and HPL-229 that are SEQ ID NO: 6 and 7, respectively of the instant application (especially page 23 at lines 23-34). WO 99/11798 A1 further teaches labeling heparanase hybridizing polynucleotide probes with fluorescent tags (i.e., light-absorbing and emitting moieties) and use in situ detection (especially page 20 and claims). WO 99/11798 A1 teaches expression of heparanase by cells of the immune system, and use of heparanase specific probes for immunodetection and diagnosis of micrometastases in biopsy specimens, i.e., in situ (especially pages 4-6 and 15).

11. Claims 4-6, 8, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/57153 A1.

WO 99/57153 A1 teaches the PCR primers HPU-355 and HPL-229 that are SEQ ID NO: 6 and 7, respectively of the instant application (especially pages 29-30 at the spanning paragraph). WO 99/57153 A1 teaches in situ hybridization with two digoxigenin (a chromogenic label) probes for detection of heparanase transcripts in normal and malignant tissues by PCR amplification (especially page 30). WO 99/57153 A1 teaches a pair of polymerase chain reaction primer sense and antisense oligonucleotides and use in PCR and detection of heparanase (especially page 23 and claims 17, 18 and 32). WO 99/57153 A1 teaches the ingredients needed for PCR include reagents for extracting mRNA from a biological sample, reagents for reverse transcribing mRNA into cDNA, a pair of heparanase specific PCR primers, nucleoside triphosphates and a thermostable DNA polymerase (especially last two paragraphs on page 23). WO 99/57153 A1 teaches a detectable moiety can be used to label a synthetic oligonucleotide of the invention, and that the detectable moiety can be radioactive isotopes, enzymes that can catalyze color or light emitting reactions and fluorophores (especially paragraph spanning pages 21 and 22).

12. Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by US 2002/0102560 A1.

US 2002/0102560 A1 teaches the PCR primers HPU-355 and HPL-229 that are SEQ ID NO: 6 and 7, respectively of the instant application (especially pages 17-18).
US 2002/0102560 A1 further teaches labeling heparanase hybridizing polynucleotide probes with fluorescent tags for in situ detection in chromosome spreads (especially page 15 and claims). US 2002/0102560 A1 teaches expression of heparanase by cells of the immune system, and use of heparanase specific probes for immunodetection and diagnosis of micrometastases in biopsy specimens, i.e., in situ (especially page 15). US 2002/0102560 A1 further teaches use of a kit for PCR amplification of heparanase cDNA, and heparanase specific sense and anti-sense primers.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 4-15 are rejected under 35 U.S.C. 103(a) as being obvious over WO 99/11798 A1 in view of RT-PCR Methods & Applications Book 1, pET System Manual 6th Edition and Ennis et al (PNAS USA 87: 2833-2837, 1990).

WO 99/11798 A1 teaches the PCR primers HPU-355 and HPL-229 which are SEQ ID NO: 6 and 7, respectively of the instant application as well as of WO 99/11798 (especially page 23 at lines 23-34). WO 99/11798 A1 further teaches labeling heparanase hybridizing polynucleotide probes such as with fluorescent tags and use in situ detection (especially page 20 and claims). WO 99/11798 A1 teaches expression of heparanase by cells of the immune system, and use of heparanase specific probes for immunodetection and diagnosis of micrometastases in biopsy specimens, i.e., in situ (especially pages 4-6 and 15).

WO 99/11798 A1 does not teach wherein either the sense or antisense oligonucleotide is labeled with a detectable moiety, including those recited in instant claims 9 and 15, nor wherein at least one of the oligonucleotides is designed having an endonuclease cleavage site.

RT-PCR Methods & Applications Book 1 teaches primer design and labeling of one or both PCT primers with radioactive detectable moiety $^{\gamma-32}$ P-ATP for quantitation of PCR-amplified products (especially pages 26 and 40).

Ennis et al teach PCR provides an approach to analyze target DNA sequences, and the use of a kit for PCR.

pET System Manual 6th Edition teaches using PCR to add restriction enzyme sites, i.e., endonuclease cleavage sites, by adding the appropriate nucleotide sequences to the primer(s) for cloning of the PCR product (page 11).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have labeled SEQ ID NO: 6 and 7 taught by WO 99/11798 A1 with the fluorescent tag taught by WO 99/11798 A1 or with the radioactive moiety taught by RT-PCR Methods & Applications Book 1, to have added a restriction enzyme site as taught by pET System Manual 6th Edition, and to have included the sense and antisense oligonucleotide PCR primers (SEQ ID NO: 6 and 7) in a kit.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to perform in situ hybridization for detecting the presence of heparanase in biopsy specimens as taught by WO 99/11798 A1 and because RT-PCR Methods & Applications Book 1 also teaches labeling of one or both PCR primers for quantitation of PCR-amplified products, and pET System Manual 6th Edition teaches addition of restriction enzyme sites for cloning of PCR product. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to perform PCR amplification more conviently for the applications taught by WO 99/11798 A1 since Ennis et al teach the advantage of using a kit for PCR amplification and WO 99/11798 A1 teaches expression of heparanase by cells of the immune system, and use of heparanase specific probes for immunodetection and diagnosis of micrometastases in biopsy specimens, i.e., in situ

15. Claims 4-15 are rejected under 35 U.S.C. 103(a) as being obvious over US 2002/0102560 A1 in view of RT-PCR Methods & Applications Book 1 and pET System Manual 6th Edition.

US 2002/0102560 A1 teaches the PCR primers HPU-355 and HPL-229 that are SEQ ID NO: 6 and 7, respectively of the instant application (especially pages 17-18).
US 2002/0102560 A1 further teaches labeling heparanase hybridizing polynucleotide probes with fluorescent tags for in situ detection in chromosome spreads (especially page 15 and claims). US 2002/0102560 A1 teaches expression of heparanase by cells of the immune system, and use of heparanase specific probes for immunodetection and diagnosis of micrometastases in biopsy specimens, i.e., in situ (especially page 15). US 2002/0102560 A1 further teaches use of a kit for PCR amplification of heparanase cDNA and heparanase specific sense and anti-sense primers.

US 2002/0102560 A1 does not teach wherein either the sense or antisense oligonucleotide is labeled with a detectable moiety, including those recited in instant claims 9 and 15, nor wherein at least one of the oligonucleotides is designed having an endonuclease cleavage site, nor wherein the PCR primer oligonucleotides are included in a kit.

RT-PCR Methods & Applications Book 1 teaches primer design and labeling of one or both PCT primers with radioactive detectable moiety gamma-32 P-ATP for quantitation of PCR-

amplified products (especially pages 26 and 40).

pET System Manual 6th Edition teaches using PCR to add restriction enzyme sites by adding the appropriate nucleotide sequences to the primer(s) for cloning of the PCR product (page 11).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have labeled SEQ ID NO: 6 and 7 taught by US 2002/0102560 A1 with the fluorescent tag taught by of US 2002/0102560 A1 or with the radioactive moiety taught by RT-PCR Methods & Applications Book 1, to have added an endonuclease cleavage site as taught by pET System Manual 6th Edition, and to have included the oligonucleotide PCR primers (SEQ ID NO: 6 and 7) in a kit as taught by US 2002/0102560 A1 for other components of the PCR amplification procedure.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to perform in situ hybridization for detecting the presence of heparanase in biopsy specimens as taught by US 2002/0102560 A1 and because RT-PCR Methods & Applications Book 1 also teaches labeling of one or more of the PCR primers for quantitation of PCR-amplified products, pET System Manual 6th Edition teaches adding restriction enzyme sites to a primer(s) for cloning of the PCR product, and US 2002/0102560 A1 teaches the use of kits for PCR amplification and one of ordinary skill in the art would recognize the convenience of using the kit for immunodetection and diagnosis of heparanase as taught by US 2002/0102560 A1.

16. Claims 4-15 are rejected under 35 U.S.C. 103(a) as being obvious over WO 99/57153 A1 in view of RT-PCR Methods & Applications Book 1, pET System Manual 6th Edition, and Ennis et al (PNAS USA 87: 2833-2837, 1990).

WO 99/57153 A1 teaches the PCR primers HPU-355 and HPL-229 that are SEQ ID NO: 6 and 7, respectively of the instant application (especially pages 29-30 at the spanning paragraph). WO 99/57153 A1 teaches in situ hybridization with two digoxigenin (a chromogenic label) probes for detection of heparanase transcripts in normal and malignant tissues by PCR amplification (especially page 30). WO 99/57153 A1 teaches a pair of polymerase chain reaction primer sense and antisense oligonucleotides and use in PCR and detection of heparanase (especially page 23 and claims 17, 18 and 32). WO 99/57153 A1 teaches the ingredients needed for PCR include reagents for extracting mRNA from a biological sample, reagents for reverse transcribing mRNA into cDNA, a pair of heparanase specific PCR primers, nucleoside triphosphates and a thermostable DNA polymerase (especially last two paragraphs on page 23). WO 99/57153 A1 teaches a detectable moiety can be used to label a synthetic oligonucleotide of the invention, and that the detectable moiety can be radioactive isotopes, enzymes that can catalyze color or light emitting reactions and fluorophores (especially paragraph spanning pages 21 and 22).

WO 99/57153 A1 does not teach wherein wherein at least one of the oligonucleotides is designed having an endonuclease cleavage site, nor wherein the primers are included in a kit.

RT-PCR Methods & Applications Book 1 teaches primer design and labeling of one or both PCT primers with radioactive detectable moiety gamma-32 P-ATP for quantitation of PCR-amplified products (especially pages 26 and 40).

pET System Manual 6th Edition teaches using PCR to add restriction enzyme sites by adding the appropriate nucleotide sequences to the primer(s) for cloning of the PCR product (page 11).

Ennis et al teach PCR provides an approach to analyze target DNA sequences, and the use of a kit for PCR.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have labeled SEQ ID NO: 6 and 7 taught by WO 99/57153 A1 with the fluorescent tag or any detectable moiety taught by WO 99/57153 A1 or with the radioactive moiety taught by RT-PCR Methods & Applications Book 1, to have added an endonuclease cleavage site as taught by pET System Manual 6th Edition, and to have included the oligonucleotide sense and antisense primers (SEQ ID NO: 6 and 7) for PCR in a kit as taught by Ennis for other components of PCR.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to perform in situ hybridization for detecting the presence of heparanase in biopsy specimens as taught by WO 99/57153 A1 and because RT-PCR Methods & Applications Book 1 also teaches labeling of one or more of the PCR primers for quantitation of PCR-amplified products, pET System Manual 6th Edition teaches adding restriction enzyme sites to a primer(s) for cloning of the PCR product, and Ennis et al teach the advantage of using a kit for PCR in order to analyze target DNA sequences. One of ordinary skill in the art would at the time the invention was made would have been motivated to do this because WO 99/57153 A1 teaches in situ hybridization for detection of heparanase transcripts in normal and malignant tissues by PCR amplification as well as the ingredients needed for PCR, and one of skill in the art would have recognized that the convenience of using a kit taught by Ennis et al would be enhanced for applications such as taught by WO 99/57153 A1.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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